REMARKS

Claims 1 to 12 appear in this application for the Examiner's review and consideration. The claims are fully supported by the specification and claims as originally filed. Therefore, there is no issue of new matter.

Applicants acknowledge with appreciation the courtesies shown to their representative, Alan P. Force (Reg. No. 39,673), in a telephone interview on March 23, 2007. The arguments set forth herein are in accordance with that interview.

Claims 1 to 12 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent Application Publication No. 2004/0181086, attributed to Javdani, Cattaneo, AN EXPERIMENT WITH ACID MINE WATER, U.S. Patent No. 4,594,466 to Reeves, Kegley, WATER TREATMENT, Hayes, 6.2.2.1, SELECTIVE PRECIPITATION, IUPAC Compendium of Chemical Terminology, (IUPAC), chm.vt.edu (VT), Angel C. de Dios, Le Chateliérs Principle, Lecture VIII, Chem 056 (de Dios), Complexation and Precipitation Titrations (Complexation), Volumetric (Titrametric) Analysis (Volumetric Analysis), Protein Purification Handbook (the Handbook), and Solubility of Ionic Salts in Water: Precipitation Titrations (Ionic Salts) for the reasons set forth on pages 2 and 3 of the Office Action.

In response, Applicants submit that the presently claimed invention is directed to a process for purifying zoledronic acid. The presently claimed process comprises: (a) raising the pH of an aqueous suspension of crude zoledronic acid until a clear solution is obtained; (b) lowering the pH of the solution obtained in (a) until purified zoledronic acid precipitates out of solution; and (c) isolating the purified zoledronic acid that has precipitated from the solution in (b). That is, in the presently claimed process, the pH of a suspension of crude zoledronic acid is raised until a clear solution is obtained; the pH of the clear solution is then lowered until purified zoledronic acid precipitates out of solution; and the precipitated purified zoledronic acid is then isolated.

One of ordinary skill in the art will recognize that, for crude zoledronic acid to be purified in the presently claimed process, impurities found in crude zoledronic acid must not dissolve with the zoledronic acid as the pH is raised to form a clear solution, and/or precipitate with the purified zoledronic acid when the pH is lowered to form a precipitate of zoledronic acid. If the impurities found in crude zoledronic acid did dissolve with the crude

zoledronic acid when the pH was raised, and then precipitated with the zoledronic acid when the pH was lowered, the suspension of crude zoledronic acid would reform without purification. Applicants respectfully submit that the cited references, whether taken alone or in combination, do not disclose or suggest anything regarding the dissolution and precipitation of zoledronic acid and the impurities found in zoledronic acid as the pH of a suspension of crude zoledronic acid is raised to form a clear solution, and the pH of the solution is lowered to precipitate purified zoledronic acid. Therefore, the cited references, whether taken alone or in combination do not disclose or suggest the presently claimed invention.

Applicants respectfully submit that the presently claimed invention also provides unexpected results. As discussed above, the cited references do not disclose or suggest that the impurities found in crude zoledronic acid do not dissolve with the zoledronic acid when the pH of a suspension of crude zoledronic acid is raised, or that the impurities found in crude zoledronic acid will not precipitate with the zoledronic acid with the pH of a solution of zoledronic acid is lowered. That is, the cited prior art references provide no evidence that the impurities of crude zoledronic acid do not go in and out of solution with the zoledronic acid as the pH is raised and lowered, so that the zoledronic acid is purified, rather than remaining in the zoledronic acid.

In this regard, the Office Action cites the discussion by de Dios of Le Chateliér's Principle in support of the rejection of the present claims. Based on Le Chateliér's Principle, one of ordinary skill in the art would not expect the presently claimed process to purify zoledronic acid. Le Chateliér's Principle states that an equilibrium is shifted from reactants to products or from products to reactants when a stress is placed on the equilibrium. That is the concentration of the products and reactants shifts in response to the stress on the equilibrium. When the stress is removed, such that the original conditions exist, the original concentrations of the reactants and products will be reestablished. In the case where the pH of a suspension is raised, such that the material in suspension is dissolved to form a clear solution, Le Chateliér's Principle teaches that the original suspension will reform when the pH is lowered to its original value.

Contrary to the statement in the Office Action dated April 13, 2006, that the impurities would remain in solution when the pH was lowered, one of ordinary skill in the

art, following the teaching of Le Chateliér's Principle, would expect the precipitation of the impurities with the zoledronic acid. That is, if all of the suspended material is dissolved by raising the pH, one of ordinary skill in the art, following the teaching of de Dios on Le Chateliér's Principle, would expect all of the material to precipitate when the pH was lowered to its original value, such that the original suspension reformed. It would be expected that all of the suspended material that dissolved when the pH was raised, would precipitate when the pH was lowered to its original value, reforming the original suspension.

Therefore, based on Le Chateliér's Principle, a suspension of crude zoledronic acid that dissolved, forming a clear solution when the pH was raised, would be expected to reform the original suspension of crude zoledronic acid when the pH was lowered to its original value. The crude zoledronic acid and any other material from the suspension that dissolved to form the clear solution would be expected to precipitate, reforming the original suspension of crude zoledronic acid when the pH was lowered to its original value. That is, at the time of the present invention, it would not have been obvious to one of ordinary skill in the art that the presently claimed process provides a purified product. Instead, based on Le Chateliér's Principle, one of ordinary skill in the art would have understood that the impurities found in crude zoledronic acid would likely precipitate with the zoledronic acid when the pH was lowered, so that the suspension of crude zoledronic acid was reformed, rather than the purified product obtained with the presently claimed invention. Therefore, de Dios does not disclose or suggest the presently claimed invention.

However, as disclosed in the present specification, the presently claimed process provides purified zoledronic acid. See Examples 1 and 2 and the table in the Detailed Description sections of the present specification. Therefore, the presently claimed invention provides unexpected results.

As further evidence of the unexpected results obtained with the presently claimed invention, Applicants submit that, prior to the present invention, zoledronic acid was purified by recrystallization from water. The prior art method, which is still used in the industrial production of zoledronic acid, is performed at reflux temperature, and requires a significantly greater quantity of water than is required with the presently claimed process. See the present specification at page 4, lines 28 to 32. As the presently claimed process has clear advantages of over the prior art process, it would be expected that the claimed process would be utilized

industrially if it was obvious to one of ordinary skill in the art. This is evidence that the presently claimed process is not obvious, as the prior art process is still used in industry for the purification of zoledronic acid.

With regard to the other references cited in the Final Office Action, those references, whether taken alone or in combination with any of the other cited references, including de Dios, do not disclose or suggest that the impurities found in crude zoledronic acid will not dissolve with the crude zoledronic acid when the pH is raised to form the clear solution, and the precipitate with the zoledronic acid when the pH is lowered to reform the suspension of crude zoledronic acid. Therefore, the cited references, whether taken alone or in combination do not disclose or suggest the presently claimed invention.

Hayes discloses the separation of impurities from leach liquors by selective precipitation. As stated at page 250 of 6.2.2, leach liquors are obtained by dissolving a mineral containing a desired metal to obtain a solution of metal ions that further comprises mineral impurities, such as ions of metals other than the desired metal. Figs. 6.2.16 and 6.2.17, for example, are directed to systems that comprise both iron and copper ions. As discussed on page 251 and Fig. 6.2.19, when the pH of the compositions of Fig. 19 are to the right of a line in that figure for a particular metal ion, that metal ion will precipitate as its metal hydroxide. Lowering the pH sufficiently, so that the conditions are to the left of the line for the metal, will cause the metal ion to go into solution. Raising the pH sufficiently will cause all of the metal ions in Fig. 6.2.19 to precipitate as their metal hydroxides, and lowering the pH sufficiently will cause all of the metal hydroxides to dissolve, reforming the solution of metal ions. The lines for Cu^{+2} and Pb^{+2} in Fig 6.2.19 are particularly close together, and will likely dissolve and precipitate together as the pH of the composition is lowered and raised. Therefore, the solutions and suspensions disclosed by Hayes cannot be purified simply by adjusting the pH until a clear solution or a precipitate is formed, as in the steps of the presently claimed invention.

Hayes does not disclose or suggest that the impurities of zoledronic acid will not dissolve when the pH is raised to form a clear solution, and precipitate with the zoledronic acid when the pH is lowered to reform the suspension of crude zoledronic acid. Therefore, Hayes does not disclose or suggest the presently claimed invention. Applicants note that they have not received a dated copy of Hayes. Therefore, Applicants do not admit that Hayes is

prior art. However, for the reasons set forth above, even if Hayes is prior art, that reference does not disclose or suggest the presently claimed invention.

As stated in the Amendment dated August 11, 2005, U.S. Patent Application Publication No. 2004/0181086, cited in the Final Office Action as Javdani, does not list Kambiz Javdani as an inventor. The inventors listed on the face of the '086 publication are Sanjay P. Godbole and Mark C. Cesa. Based on the statement in the Office Action dated February 22, 2005, that the '086 publication clearly teaches the crystallization of 2-nitro-4-methylsulfonylbenzoic acid, Applicants believe that the intended citation is U.S. Patent Application No. 10/472,962, published as 2004/0171872 to Kamiz Javdani.

The '086 publication discloses a process for the recovery of nitrite monomer from the reactor effluent of an ammoxidation of propylene, propane, isobutane, or isobutylene in the production of acrylonitrite or methacrylonitrite. Page 1, paragraph [0002]. The processes used in the commercial recovery of ammoxidation processes utilize one or more distillations to purify the products. Page 1, paragraph [0003]. The separation in the recovery column of the distillation apparatus is "greatly affected by the pH of the system," such that the pH should be maintained in the range of about 5.5 to 7.5. Page 1, paragraph [0007]. The '086 publication discloses "an improved extractive distillation process for the recovery of acrylonitrite or methacrylonitrite wherein the pH of the recovery column is maintained near neutral."

The '086 publication does not disclose or suggest the dissolution or precipitation of any substance by adjusting the pH of a suspension or solution of the substance. In particular, the '086 publication does not disclose or suggest that the impurities found in zoledronic acid do not dissolve and precipitate with zoledronic acid as the pH is raised and lowered. Therefore, the '086 publication does not disclose or suggest the presently claimed invention.

As discussed above, Applicants believe that the disclosure attributed to the '086 publication in the Final Office Action should be attributed to U.S. Patent Application No. 10/472,962 to Javdani et al. (Javdani), which was published as U.S. Patent Application Publication No. 2004/0171872. Javdani discloses a process for the preparation of mesotrione that is free of impurities that give a positive result for mutagens in the Ames test. Javdani, page 1, paragraph [0006]. Reportedly, the mutagenic impurities are not a result of the known process for preparing mesotrione. Instead, the impurities are present in the

2-nitro-4-methylsulfonylbenzoic acid (NMSBA) starting material, and are carried over to the final product. Id.

Javdani discloses a process for the removal of the impurities from the NMSBA starting material. The disclosed process comprises at least two of the following steps in any order:

(a) dissolving 2-nitro-4-methylsulfonylbenzoic acid in water at a pH of about 2 to 10, followed by filtration;

(b) contacting an aqueous solution of 2-nitro-4-methylsulfonylbenzoic acid with activated carbon at a pH of about 2 to 10; and

(c) treating an aqueous solution of 2-nitro-4-methylsulfonylbenzoic acid with sufficient base to hydrolyze undesired nitro and dinitro substituted impurities. Javdani, paragraphs [0007] to [0010].

Those steps are followed by maintaining the resulting aqueous solution comprising 2-nitro-4-methylsulfonylbenzoic acid at a temperature of up to about 95°C, and adjusting the pH of the solution to about a pH which is sufficient to effect crystallization of 2-nitro-4-methylsulfonylbenzoic acid upon cooling. Javdani, paragraph [0011]. The preferred pH for the dissolution of NMSBA is about 3 to 7, i.e., from acidic to neutral. The disclosed process is a salting-out procedure, which is outside the scope of the present claims.

Javdani does disclose that a solution of NSMBA can be acidified and cooled to precipitate the NMSBA. However, Javdani does not disclose or suggest that impurities found in crude zoledronic acid do not dissolve with the crude zoledronic acid when the pH of a suspension of crude zoledronic acid is raised to form a clear solution and precipitate with the zoledronic acid when the pH is lowered. One of ordinary skill in the art will understand that a process for purifying one organic acid will not necessarily purify a second, different organic acid. Therefore, Javdani does not disclose or suggest the presently claimed invention.

Cattaneo discloses that coal placed in water releases iron ions into the water, and lowers the pH. Cattaneo also discloses that adding limestone to the resulting acidic water neutralizes the acidity, and precipitates iron. Cattaneo does not disclose that the impurities found in crude zoledronic acid do not go into solution with the zoledronic acid when the pH is raised, and precipitate with the zoledronic acid when the pH is lowered. Therefore, Cattaneo does not disclose or suggest the presently claimed invention.

Reeves discloses a process for the recovery of weak organic acids, such as ethanol and methanol, from aqueous solutions of fermentation products for use as fuels. As will be recognized by one of ordinary skill in the art, alcohol is miscible in water at any pH, and, thus, forms a solution, not a suspension. Reeves does not disclose or suggest that a suspension of the disclosed alcohols is converted to a clear solution by raising the pH, or that an alcohol can be precipitated by lowering the pH of an alcohol water solution. Instead Reeves discloses causing a phase separation by adding a sufficient amount, at least 26g/100ml, of a base or basic salt to create a saturated solution of the base or salt. As the water becomes saturated with the base or salt, the base or salt replaces the alcohol in the solution, causing the phase separation.

This is not the presently claimed invention. Reeves does not disclose or suggest that the impurities found in crude zoledronic acid do not go into solution with the zoledronic acid when the pH is raised, and precipitate with the zoledronic acid when the pH is lowered. Therefore, Reeves does not disclose or suggest the presently claimed invention.

Kegley discloses what appears to be questions for a series of lesson plans that use water treatment to teach basic chemical principles, such as solubility, analytical methods for determining amounts of dissolved materials in water, equilibrium, Le Chateliér's principle, acids, bases, and pH. Kegley also provides animations of the dissolution of sodium chloride in water, the precipitation of copper ions with iodate ions, and two equilibrium simulators on the atomic scale. Kegley does not disclose or suggest that the impurities found in crude zoledronic acid do not go into solution with the zoledronic acid when the pH is raised, and precipitate with the zoledronic acid when the pH is lowered. Therefore, Kegley does not disclose or suggest the presently claimed invention.

IUPAC defines titrations as a process of determining the quantity of a substance A by adding measured increments of substance B, with which it reacts. The present invention is not a titration, and many titrations do not result in precipitation. IUPAC does not disclose or suggest that the impurities found in crude zoledronic acid do not go into solution with the zoledronic acid when the pH is raised, and precipitate with the zoledronic acid when the pH is lowered. Therefore, IUPAC does not disclose or suggest the presently claimed invention.

VT similarly defines titrations. Again, The present invention is not a titration, and many titrations do not result in precipitation. VT does not disclose or suggest that the

impurities found in crude zoledronic acid do not go into solution with the zoledronic acid when the pH is raised, and precipitate with the zoledronic acid when the pH is lowered. Therefore, VT does not disclose or suggest the presently claimed invention.

Complexation discloses the formation of metal complexes, as well as precipitation titrations using silver ion. Complexation does not disclose or suggest that the impurities found in crude zoledronic acid do not go into solution with the zoledronic acid when the pH is raised, and precipitate with the zoledronic acid when the pH is lowered. Therefore, Complexation does not disclose or suggest the presently claimed invention.

Volumetric Analysis discloses titrations and volumetric, i.e., titrimetric, analysis. Volumetric Analysis does not disclose or suggest that the impurities found in crude zoledronic acid do not go into solution with the zoledronic acid when the pH is raised, and precipitate with the zoledronic acid when the pH is lowered. Therefore, Volumetric Analysis does not disclose or suggest the presently claimed invention.

The Handbook discloses various strategies for the purification of proteins. The Handbook does not disclose or suggest that the impurities found in crude zoledronic acid do not go into solution with the zoledronic acid when the pH is raised, and precipitate with the zoledronic acid when the pH is lowered. Therefore, the Handbook does not disclose or suggest the presently claimed invention.

The reference Ionic Salts defines titrations, discloses the determination of chloride ion concentration by titration with silver ion, and defines pH and endpoints. Ionic Salts does not disclose or suggest that the impurities found in crude zoledronic acid do not go into solution with the zoledronic acid when the pH is raised, and precipitate with the zoledronic acid when the pH is lowered. Therefore, Ionic Salts does not disclose or suggest the presently claimed invention.

Therefore, the cited references, whether taken alone or in combination do not disclose or suggest a process for purifying zoledronic acid, comprising the steps of the presently claimed process, and, thus, the claims are not obvious over those references. Accordingly, it is respectfully requested that the examiner withdraw the rejection of claims 1 to 12 under 35 U.S.C. § 103(a) over Javdani, Cattaneo, Reeves, Kegley, Hayes, IUPAC, VT, de Dios, Complexation, Volumetric Analysis, the Handbook, and Ionic Salts.

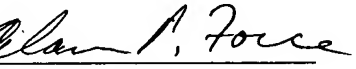
Applicants thus submit that the entire application is now in condition for allowance, an early notice of which would be appreciated. Should the Examiner not agree with Applicants' position, a personal or telephonic interview is respectfully requested to discuss any remaining issues prior to the issuance of a further Office Action, and to expedite the allowance of the application.

No fee is believed to be due for the filing of this Amendment. A Request for Continued Examination is filed herewith. Should any other fees be due, however, please charge such fees to Deposit Account No. 11-0600.

Respectfully submitted,

KENYON & KENYON

Dated: April 5, 2007

By: 

Alan P. Force
Reg. No. 39,673
One Broadway
New York, NY 10004
(212) 425-7200